NEW ROOT OF SYNTHESIS OF SUBSTITUTED 2-PYRAZOLINES

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ABSTRACT

The 1-(4/-chloro phenyl)-3-(3/-nitro phenyl)-prop-2-en-1-one 1(a-h) was obtained by reaction of different acetophenone and aromatic aldehydes in the presence of aqueous sodium hydroxide solution. A mixture of 1-(4/-chloro phenyl)-3-(3/-nitro phenyl)-prop-2-en-1-one 1(a-h), Hydrazine hydrate and glacial acetic acid give 1-acetyl-3-(4/-chloro phenyl)-5-(3/-nitro phenyl)-2-pyrazoline 2(a-h). 1-[3/-(4//-dimethyl amino phenyl)-prop-2/-en-1/-one]-3-(4/- chloro phenyl)-5-(3/-Substituted phenyl)-2-pyrazoline 3(a-h) was obtain by reaction of 2(a-h) with guanidine carbonate and NaOH was dissolved in DMF to form 1-[3/-(4//-dimethyl amino phenyl)-5/-amino pyrimidine]- 3-(4/- chloro phenyl)-5-(3/-Substituted phenyl)-2-pyrazoline 4(a-h).The newly synthesized compounds show antibacterial and antifungal activities when compared with standard drug Norfloxacine and Griseofulvin against Bacterial cultures such as *E. coli*, *Pseudomonas aeruginosa*, S. aureus, *Proteus vulgaris* and fungal cultres Aspergillus niger and *Candida albicans*. The synthesized compounds are characterized by FTIR, ^{1}H NMR, elemental analysis, chemical properties.

Keywords: Phenyl amino, Phenylprop-2-en-1-one, Azomethine, Pyrimidines.

INTRODUCTION

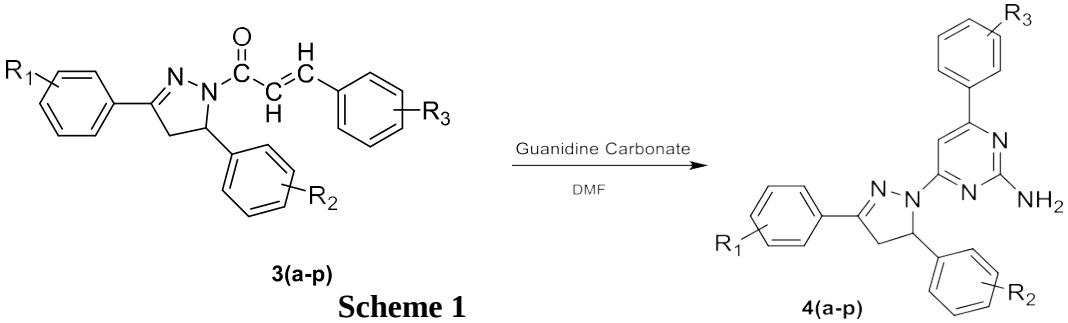
Heterocyclic compounds have been found to occur widely in nature and have proved to be often immense significance on life. Their varied physicochemical and pharmacological properties attract the attention of chemists and biologists. They have gained much importance in medicinal chemistry due to their presence in a large number of pharmacologically active moieties and are in regular clinical use and proved to be a potent drug. Common drugs such as morphine, penicillin and non-steroidal anti-inflammatory agents contain at least one hetero atom in their structure[1]. Besides clinical use, they are also applicable in the field of agricultural, photography, dyes, biocides and polymer science. The range of known compounds is virtually limitless owing to an impressive spectrum of physical, chemical and biological properties[2]. The development of a clean procedure for the preparation of heterocyclic compound is a major challenge in modern heterocyclic chemistry in view of the environmental, practical and economical issues. Among different heterocyclic system, the chemistry of five and six membered heterocycles with more than one hetero atom has gained significance as many of them exhibit pronounced bioactive nature. In the present study, considerable attention has been focused on the pyrazolines, chalcones and pyrimidines because of their fascinating biological activities. 2-Pyrazolines five membered heterocyclic compounds with two hetero atoms are termed Azoles[3]. They comprise the several ring systems which are essential for the living systems. The lone pair of electrons on the hetero atom contributes towards the aromatic sextet. Azoles containing two nitrogen atoms in the 1, 2- position are termed as pyrazole 1 with molecular formula $C_3H_4N_2$, discovered by Buchner in 1889. The dihydro pyrazoles are called Pyrazolines introduced by Fischer and

Knovenagel[4] in the late 19th century by the reaction of acrolein with phenyl hydrazine which was reported as the first experiment for the synthesis of 2-pyrazoline, by using α, β – enone and hydrazine derivatives. Later it was corroborated by Auwers et al[5, 6].

Five membered heterocyclic molecules, 2-pyrazoline, containing two nitrogen atoms in adjacent position and possessing only one endocyclic double bond has gained attraction and possess a broad spectrum of biological activity such as antimicrobial[7], antimycobacterial[8], anti-depressant[9], anti-inflammetory[10], analgesic[11], anticonvalsant[12], anticancer[13], antitumor[14], cytotoxic[15], antioxidan[16], antiamoebic[17], antiproliferative[18], hypotensive activity[19], antiepileptic[20] and insecticidal properties[21].

RESULT AND DISCUSSION

The precursor chalcones **1a** is synthesized by a base catalyzed Claisen– Schmidt condensation reaction of 4-chloro acetophenone and 3-nitro benzaldehyde with 93% yield. The synthesis of chalcones **1a** was confirmed on the basis of its IR and ^{1}H NMR spectra. The IR spectrum of a compound **1a** taken in KBr pellet showed an absorption band at 1667.5 cm^{-1} indicating the presence of conjugated carbonyl group (C=O). The ^{1}H NMR spectrum displayed 2 doublets at δ7.82 ppm (H- α) and δ 8.09 ppm (H-β) which confirm the formation of chalcones possessing a α, β – unsaturated ketones. The other aromatic protons usually appear in between δ7.58-8.74 ppm depending on the type of aromatic ring and electronic effects of the substituent's present on these rings. The ^{13}C NMR spectrum was consistent with the ^{1}H NMR spectrum. The result of elemental analysis and mass spectrum was in agreement with those of calculated values. The reaction of 1-[3/-(4//-dimethyl amino phenyl)-prop-2/-en-1/-one]-3- (4/-chloro phenyl)-5-(3/-nitro phenyl)-2-pyrazoline **3p** with guanidine carbonate in DMF in presence of NaOH gave product 1-[3/-(4//-dimethyl amino phenyl)-5/-amino pyrimidine]-3-(4/- chloro phenyl)-5-(3/-nitro phenyl)-2-pyrazoline **4p**. The IR spectrum of a compound **4p** taken in KBr pellet exhibited two peaks at 3523.21 cm^{-1} and 3405.23 cm^{-1} showed the presence of a primary amino group. The C=O stretching vibration is absent, indicating the cyclisation of chalcone into pyrimidine ring. The peaks in the region 1663.1 cm^{-1} and 1550.1 cm^{-1} shows the presence of C=N and C=C group. The ^{1}H NMR spectrum shows the multipletes in the range 8.13-6.65 due to aromatic protons. The singlet at 4.62 and 3.04 shows the presence of NH_2 and $N(CH_3)_2$ protons. The ^{13}C NMR spectrum showed singlet at δ 93.47, δ 59.61, δ 41.08, δ 40.03 ppm shows the presence of C_2 pyrimidine, C_5 pyrazoline, C_4 pyrazoline and $N(CH_3)_2$ carbon atoms. The ^{13}C NMR spectrum is consistent with the ^{1}H NMR spectrum. The result of elemental analysis and mass spectra was in agreement with those of calculated values. IR spectrum confirms the presence of particular functional groups and mass spectrum confirmed the molecular weight of **4p**. Based on above spectral data, the structure of compound **4p** is confirmed as 1-[3/-(4//-dimethyl amino phenyl)-5/- amino pyrimidine]-3-(4/- chloro phenyl)-5-(3/-nitro phenyl)-2-pyrazoline **4p**.



3(a-p) 4(a-p)

Scheme 1

Where,

ID	R_1	R_2	R_3	ID	R_1	R_2	R_3
4a	4-NO_2	4$N(CH_3)_2$	4-OH	4i	4-Cl	3-NO_2	4-OCH_3
4b	4-NO_2	4$N(CH_3)_2$	4-OCH_3	4j	4-Cl	3-NO_2	3-NO_2
4c	4-NO_2	4$N(CH_3)_2$	3- NO_2	4k	4-Cl	3-NO_2	4-$N(CH_3)_2$
4d	4-NO_2	4$N(CH_3)_2$	4-$N(CH_3)_2$	4l	4-NO_2	4-OH	2,4(Cl)2
4e	4-NO_2	3-NO_2	4-OH	4m	4-OH	H	4-$N(CH_3)_2$
4f	4-NO_2	3-NO_2	4-OCH_3	4n	4-OH	4-OCH_3	4-OH
4g	4-NO_2	3-NO_2	3- NO_2	4o	4-Cl	4N(CH3)2	4-$N(CH_3)_2$
4h	4-Cl	3-NO_2	4-OH	4p	4-Cl	4N(CH3)2	4-OCH_3

BIOLOGICAL STUDIES

Comparative study of 1-[3/-(4//-dimethyl amino phenyl)-5/-amino pyrimidine]- 3-(4/- chloro phenyl)-5-(3/-Substituted phenyl)-2-pyrazoline **4(a-p)** have been observed by using Norfloxacine and Griseofulvine as standards. The enhancement in biological activity of compound (1) as compared with the newly synthesized **(4a-p)** has been observed. The synthesized compounds were tested at 100g/ml concentration against Escherichia *coli*, Staphylococcus *aureus*, Ps. *acruginosa*, P.*vulgaris*, A. *niger* and C. *albicans* for its antibacterial and antifungal screening as shown in **Table-I.**

Table 1: The *In Vitro* antibacterial & antifungal activities of compounds **4(a-p)**

S.No.	Derivative	Diameter of zone of inhibition (mm) for organism				
		Bacterial Strains				Fungal strains
		Gram negative		Gram positive		
		E.Coli	P.Aeruginosa	S. Aureus	B.Subtilis	A.Niger
1	4a	15	18	21	10	19
2	4b	15	19	20	11	18
3	4c	13	18	21	11	15
4	4d	18	22	22	15	19
5	4e	16	19	19	12	14
6	4f	14	18	20	14	16
7	4g	13	19	18	11	14
8	4h	16	20	18	12	16

9	4i	17	18	20	13	16
10	4j	15	19	18	10	17
11	4k	18	20	19	10	19
12	4l	20	21	21	21	23
13	4m	15	20	20	14	12
14	4n	19	20	19	13	19
15	4o	18	19	19	12	18
16	4p	18	20	20	13	18
17	Ciprofloxacin	48	51	41	40	--
18	Fluconazole	--	--	--	--	40

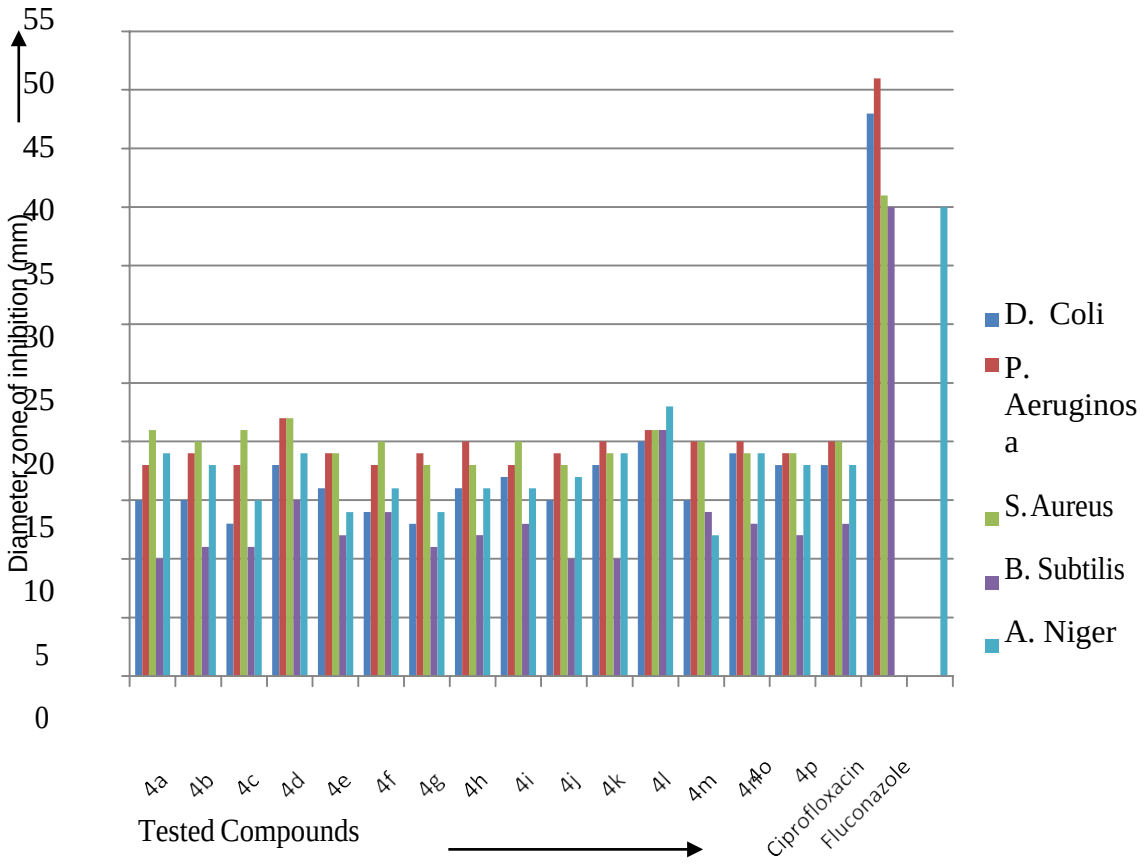


Fig. 1 : Antibacterial & antifungal activities of compounds **(a-p)**

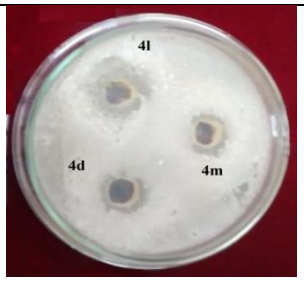
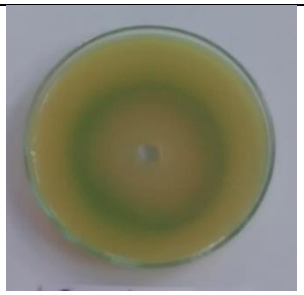
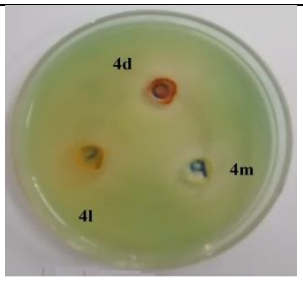
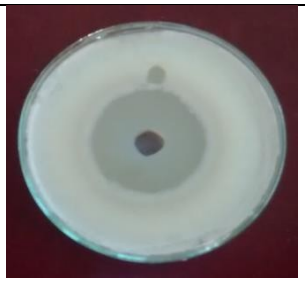
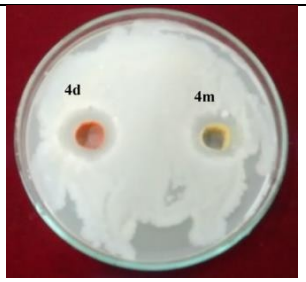
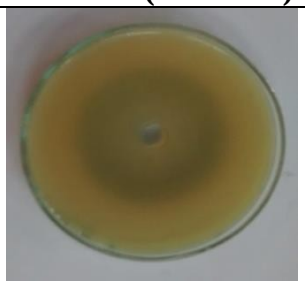
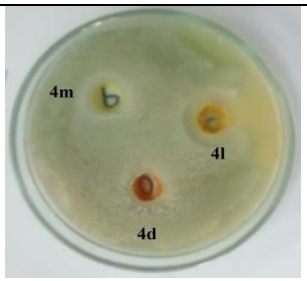
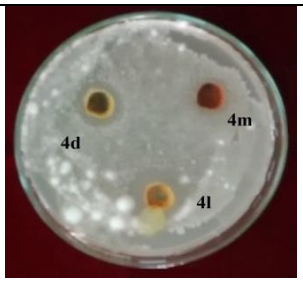
 **E-Coli (Standard)**	 **E-Coli**
 **P. Aeruginosa(Standard)**	 **P. Aeruginosa**
 **S. Aureus (Standard)**	 **S. Aureus**
 **B. Subtilis (Standard)**	 **B. Subtilis**
 **A. Niger (Standard)**	 **A. Niger**

Fig 2 : Photographs showing zone of inhibition of 4d, 4m, 4l & standards.

EXPERIMENTAL

Synthesis of 1-(substituted phenyl)-3-(substituted phenyl) prop-2-en-1-one 1 (a-h)

Equimolar quantities of different acetophenone (0.01 mole) and aromatic aldehydes (0.01 mole) were dissolved in minimum amount of alcohol. To this, aqueous sodium hydroxide solution (10 ml, 40%) was added drop wise with stirring. The reaction mixture was stirred vigorously for 2-3 hours, below 25^0c, until the mixture is so thick that stirring is no longer effective and neutralized with conc. HCl. The solid obtained was filtered washed with cold water, until the washings are neutral to litmus.

Synthesis of 1-acetyl-3-(substituted phenyl) -5- (substituted phenyl)-2-Pyrazolines 2(a-h).

A mixture of chalcones (10 mmoles), 99% Hydrazine hydrate (50 mmole) and glacial acetic acid (60 ml) was refluxed for 3-6 hour in water bath, then poured on to crushed ice. The resulting solid was washed and crystallized with suitable solvent.

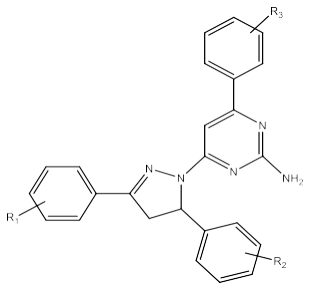
Synthesis of 1-[3/-(substituted phenyl) prop-2/-en-1/-one]-3- (substituted phenyl)-5-(substituted 3 (a-p). phenyl)-2-pyrazoline

The substituted phenyl)-5-(substituted phenyl) - 2-pyrazolines 2(a-h) (0.01 mole) and different aromatic aldehydes adopted for the synthesis of acetyl pyrazoline derivatives. The reaction mixture was stirred vigorously for 2-3 hours and neutralized with concentrated hydrochloric acid. The solid obtained was washed with cold water and recrystallized with suitable solvent**.**

Synthesis of 1-(3/-substituted phenyl-5/-amino pyrimidine) - 3-(substituted phenyl)-5-(substituted phenyl)-2-pyrazolines 4 (a- p).

A mixture of 1-(substituted chalcones)-3-(substituted phenyl)–5-(substituted phenyl)-2-pyrazoline **3(a-p)** (0.01mole), guanidine carbonate (0.01mole) and NaOH (0.01mole, 0.4 g) was dissolved in DMF (40 ml). The reaction mixture was stirred and refluxed for 3-5 hours on the water bath and the completion of the reaction is monitored by TLC then poured on to crushed ice. The solid obtained was washed with cold water and purified by recrystallization from ethanol.

Table 2: Physicochemical characterization data of compound **4(a-p)**



ID	R1	R2	R3	Molecular Formula	MP 0_C	Yield %	Analysis Cal (found) C %	H %	N %
4a	4-NO2	4N(CH3)2	4-OH	C27H25N7O3	132	66	65.45 (65.44)	5.05 (5.09)	19.80 (19.88)
4b	4-NO2	4N(CH3	4-OCH3	C28H27N7O3	147	70	66.01 (66.10)	5.31 (5.39)	19.25 (19.32)

		)2							
4c	4-NO2	4N(CH3)2	3- NO2	C27H24N8O4	85	71	61.83 (61.79)	4.58 (4.65)	21.37 (21.39)
4d	4-NO2	4N(CH3)2	4-N(CH3)2	C29H30N8O2	110	76	66.67 (66.64)	5.75 (5.78)	21.46 (21.51)
4e	4-NO2	3-NO2	4-OH	C25H19N7O5	78	82	60.36 (60.30	3.82 (3.90)	19.72 (19.66)
4f	4-NO2	3-NO2	4-OCH3	C26H21N7O5	80	76	61.06 (61.11)	4.11 (4.09)	19.18 (19.21)
4g	4-NO2	3-NO2	3- NO2	C25H18N8O6	74	67	57.03 (57.10)	3.42 (3.49)	21.29 (21.22)
4h	4-Cl	3-NO2	4-OH	C25H19N6O3Cl	148	65	61.73 (61.68)	3.91 (3.99)	17.28 (17.23)
4i	4-Cl	3-NO2	4-OCH3	C26H21N6O3Cl	97	67	62.40 (62.39)	4.20 (4.25)	16.80 (16.75)
4j	4-Cl	3-NO2	3- NO2	C25H18N7O4Cl	109	59	58.25 (58.23)	3.50 (3.48)	19.03 (19.08)
4k	4-Cl	3-NO2	4-N-(CH3)2	C27H24N7O2Cl	76	62	63.16 (63.18)	4.68 (4.69)	19.10 (19.14)
4l	4-NO2	4-OH	2,4-(Cl)2	C25H18N6O3Cl2	135	58	57.58 (57.62)	3.46 (3.44)	16.12 (16.15)
4m	4-OH	H	4-N(CH3)2	C27H26N6O	117	57	72.0 (72.10)	5.78 (5.75)	18.67 (18.70)
4n	4-OH	4-OCH3	4-OH	C26H23N5O3	124	60	68.87 (68.89)	5.07 (5.10)	15.45 (15.60)
4o	4-Cl	4N(CH3)2	4-N(CH3)2	C29H30N7Cl	74	61	68.10 (68.09)	5.87 (5.89)	19.18 (19.20)
4p	4-Cl	4N(CH3)2	4-OCH3	C28H27N6OCl	112	64	67.47 (67.44)	5.42 (5.48)	16.87 (16.91)

1) **Elemental Analysis:** From the analytical data the molecular formula of the compound **1a** was found to be C15H10NO3Cl. Calculated : %C- 62.72 %H – 3.48, %N – 4.89; Found %C – 62.68, %H – 3.42, %N -4.85

Spectral Analysis:

FTIR (KBr, λ max, cm^{-1}): 3091.32 (Ar-H str), 3066.25, 3035.3 (=C-H, H-C= str), 1667.5 (C=O str), 1608.5, 1588.8 (C=C str), 1523.2, 1351.2 (Ar-NO2 str), 742.13 (Ar-Cl)

^{1}H NMR (δ ppm): 7.58-8.74 (m, 8H, Ar-H), 8.09 (d, 1H, H β), 7.82 (d, 1H, H α).

^{13}C NMR (δ ppm): 187.69 (C=O), 146.44(=CH-), 122.49 (-CH=), 121.13-141.69 (12C,Aromatic)

Mass Spectra: m/z 288.27. It showed several other peaks at m/z 166.35, m/z 155.33, m/z 122.02, m/z 111.22 etc.

Elemental Analysis: C17H14N3O3Cl. Calculated : %C- 59.48,

%H – 4.08 , %N – 12.24 ; Found %C – 59.42, %H – 4.10 , %N – 12.19.

Spectral Analysis:

FTIR (KBr, λ max, cm^{-1}): 3082.28 (Ar-H str), 2935.32, 2866.33 (C-H str), 1670.3 (C=O str), 1596.16 (C=N str), 1480.22 (C=C str), 1351.63 (Ar- NO_2 str), 1150.21 (C-N str), 740.25 (C-Cl str).

^{1}H NMR (δ ppm): 7.42-8.10 (m, 8H, Ar-H), 5.69-5.73 (dd, 1H, C_5 pyrazoline), 3.87-3.94 (dd, 1H, C_4cis pyrazoline), 3.16-3.22 (dd, 1H, C_4trans pyrazoline), 2.38 (s, 3H, CH_3).

^{13}C NMR (δ ppm):167.10 (C=O), 152.43 (C_3 Pyrazoline), 120-147 (12C, phenyl ring), 58.91 (C_5 pyrazoline), 41.51 (C_4 pyrazoline), 21.10 (CH_3).

Mass Spectra: m/z 344.32. It showed several other peaks at m/z 232.32, m/z 123.02, m/z 111.05 etc.

Elemental Analysis: From the analytical data the molecular formula of the compound **3k** was found to be $C_{26}H_{23}N_4O_3Cl$. Calculated: %C- 65.82, %H – 4.85, %N – 11.81; Found %C – 65.78, %H – 4.90, %N – 11.83.

Spectral Analysis:

FTIR (KBr, λ max, cm^{-1}):

3523.21, 3405.23 (NH_2 str), 3086.19, 3049.18 (Ar-H str), 2908.9, 2821.10 (C-H str), 1663.1, 1599.02 (C=N str), 1505.1 (C=C str), 1535.1, 1370.1 (Ar-NO_2 str), 1163.01 (C-N str), 726.9 (C-Cl str).

^{1}H NMR (δ ppm): 8.13-6.65 (m, 13H, Ar-H), 5.70-5.66 (dd, 1H, C_5 pyrazoline), 4.62 (s, 2H, -NH2), 3.72-3.65 (dd, 1H, C_4cis pyrazoline), 3.23-3.18 (dd, 1H, C_4trans pyrazoline), 3.04 (s, 6H, $N(CH_3)_2$).

^{13}C NMR (δ ppm): 165.02 (C_1 pyrimidine), 162.59 (C_5 pyrimidine), 158.75 (C_3 pyrimidine), 152.43 (C_3 pyrazoline), 154.85-110.10 (18C, phenyl ring), 93.47 (C_2 pyrimidine), 59.61 (C_5 pyrazoline), 41.08 (C_4 pyrazoline), 40.03 (N (CH_3)2).

Mass Spectra (δ ppm): m/z (M^+) : m/z 301.19, m/z 222.47, m/z190.16 m/z 121.31, m/z 112.44 etc.

CONCLUSION

It is concluded for scheme that and efficient method for the synthesis of 1-[3/-(4//-dimethyl amino phenyl)-5/-amino pyrimidine]- 3-(4/-chloro phenyl)-5-(3/-Substituted phenyl)-2-pyrazoline **4(a-p)**with excellent yield have been developed. The result of this study indicate that the present synthetic method is a simple efficient, inexpensive and easy synthesis of biologically active compounds 1-[3/-(4//-dimethyl amino phenyl)-5/-amino pyrimidine]-3-(4/- chloro phenyl)-5-(3/-Substituted phenyl)-2-pyrazoline **4(a-p)**. These compounds showing good result tested at 100 mg/ml concentration against E. coli, S. aureus, Ps. acruginosa, P. vulgaris, A. niger and C. albicans as compare to simple di-amine.

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